# Selecting the Right Solid Form - Faster, Smarter, Better

Shanming Kuang, Ph.D.

Harsh S. Shah, Ph.D.

Fei Sheng, Ph.D.

# Introduction

Drug molecules can crystallize in a variety of solid forms, including polymorph, hydrate, solvate, salt and cocrystal, or solidify as amorphous materials (Figure 1). Polymorphs are crystal structures with the same chemical composition but different arrangements and/or conformations of the molecules in the crystal lattice. Solvates/hydrates are crystal forms incorporated with water/solvent molecules. Crystalline salts are composed of ionizable drug substance and counterion, while cocrystals are crystalline materials made of drug substances and cocrystal coformers in a specific stoichiometric ratio excluding solvates and salts. Amorphous materials are solid substances that lack a defined, long-range ordered structure but exhibit disordered arrangement of molecules, which are high energy metastable form. One of the most common approaches to stabilize amorphous systems is to make an amorphous solid dispersion, a single amorphous phase containing both drug molecule and polymer that are dispersed at a molecular level.

Various solid forms of a drug substance can have distinct chemical and physical properties, including crystallinity, hygroscopicity, chemical reactivity, apparent solubility, dissolution rate, and stability. These properties may have a direct effect on the manufacturability of the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, different solid forms can affect the quality, safety, and efficacy of the drug product. Because energy differences between solid forms are usually relatively small, form interconversion is common. Form changes can occur during routine API manufacturing operations and/or drug product processes, storage, and use. The appearance of a new solid form during late stages of development may delay filing and a new form discovery in drug products may lead to drug product recalls. A well-known example is Ritonavir which is an antiretroviral agent for HIV-1 infection, introduced to the market in 1996 as a capsule with only one known Form I. Two years later, capsules began failing dissolution specification by ~50% due to the unexpected appearance of a more stable and less soluble Form II. As a result, the capsules were discontinued, putting patients at risk and leading to $250M in financial losses.

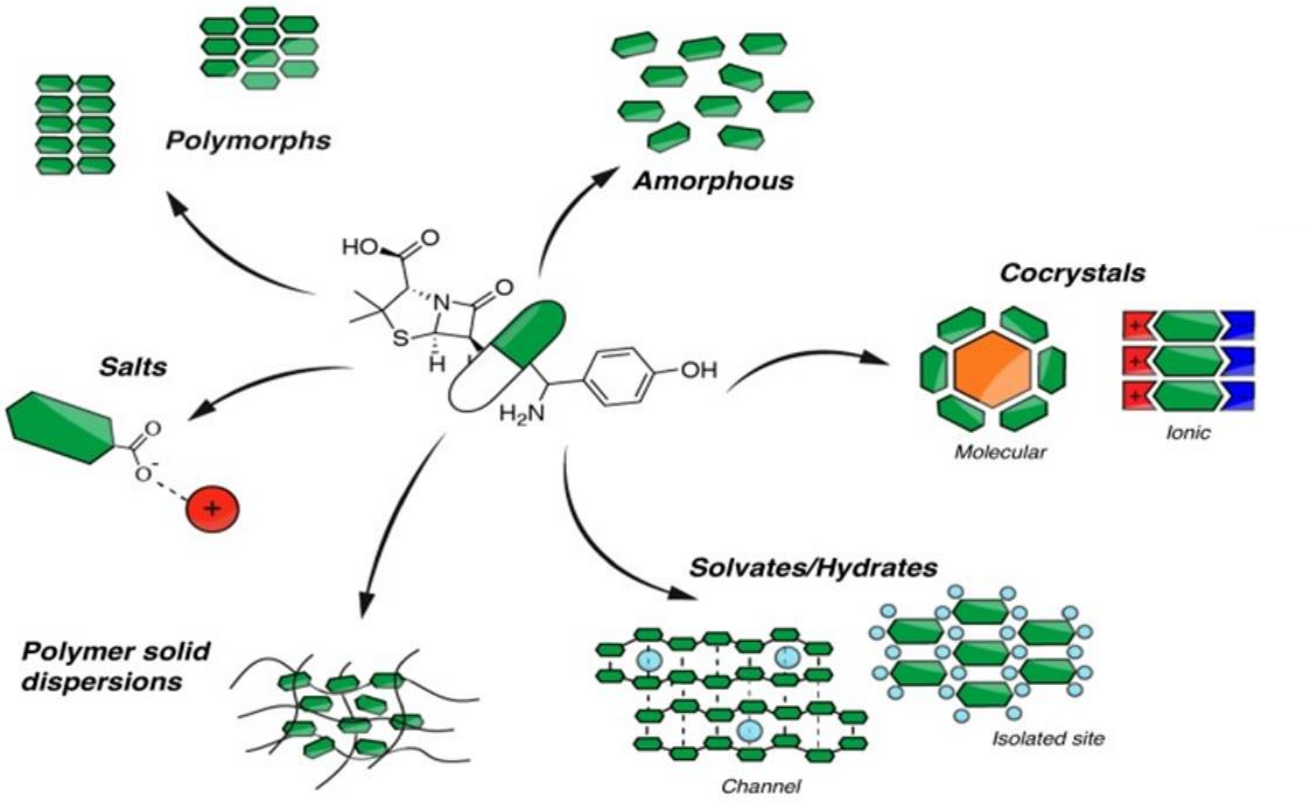


Figure 1. Solid Forms of Drug Molecules
Data derived from Drug Discovery Today Volume 24, Number 3 March 2019

Patent protection of solid forms in addition to the primary drug molecules has proved to be advantageous for pharmaceutical companies because it is a good strategy to extend patent life.[1] One example was Atorvastatin which is a block buster drug marketed by Pfizer under the brand name of Lipitor. The company filed a specific chemistry patent for Atorvastatin calcium in 1991 that expired in 2011. To further extend market rights, Pfizer filed another patent, disclosing the drugs novel polymorphs in 1996 which expired in 2017. Through this strategy, the company was able to extend market exclusivity by six additional years. The strategy was followed by many pharmaceutical companies who tend to file the polymorph patent as a separate patent. As in the case of sitagliptin, new polymorphic patents are now commonly used to stop generic companies from entering the market. To bring generic drugs to market, generic companies must either look for a new and stable polymorph or wait for the polymorph patent to expire. On the other hand, in the case of Paxil, SmithKline's U.S. patented only covered crystalline paroxetine hydrochloride hemihydrate in a US Patent. As a result, Apotex was able to market a drug containing anhydrate with no patent infringement.

From a regulatory standpoint, FDA and ICH guidelines both provide decision trees that can be followed in determining if a specification is required to confirm the nature of the polymorph present in both drug substance and product. These decision trees represent the current strategy for assessing potential concerns associated with polymorphic forms in drug products. The decision trees either eliminate the risk of potential solid forms or demonstrate that the manufacturer has control of the solid form throughout the process.

Therefore, it is critical to identify and select the optimal form during early drug development. A solid form with acceptable solid-state properties, such as crystallinity, hygroscopicity, solubility, stability and processability, mitigates risks in drug product failure during development or commercialization. A thorough solid form investigation also provides rationale for form selection as required by regulatory filing.

## Form Screen and Selection

At Porton J-Star, we employ an integrated approach to identify and select the most suitable solid form for development (Figure 2). We conduct effective screen and rigorous assessments for polymorphs, salts, cocrystals, as well as amorphous solid dispersions, by applying our comprehensive expertise and experience.

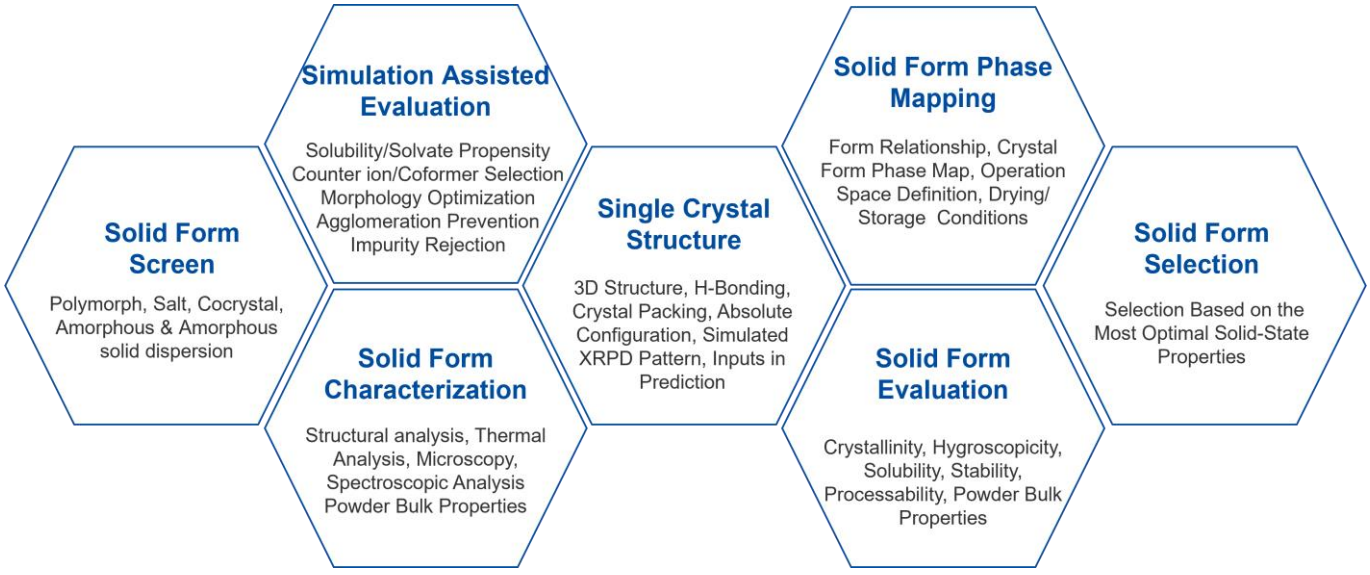


Figure 2. Integrated Approaches for Solid Form Screen & Selection

1. We apply rational design of form screening using our rich experience based on development phase and simulation results. Over the years, we have worked on solid form screen and selection for more than 1000 drug candidates. We maximize the chance of finding possible solid form by selecting the appropriate solvents, counter ions, cocrystal coformers and crystallization methods. We maximize screen space by diversifying screen methods instead of repeating a large number of experiments with the same method. We utilize prediction to assist selection of solvents, counter ions and coformers to increase the success rate. For instance, we have developed a new methodology for solvent selection of salt/cocrystal crystallization by taking into consideration of solubility, ionization potential and congruent phase diagrams.[2] In another example, we developed a novel virtual coformer screening model (Figure 3), COSMO-RS + Δ-ML, integrating COSMO-RS with machine learning to account for both miscibility in the amorphous phase and crystallinity contributions to cocrystallization.[3] This computational approach was validated against published experimental cocrystal screening data for multiple APIs, demonstrating superior performance compared with the pure COSMO-RS method. We design screen activities based on the development phase of the drug candidates. In the early phase of IND (investigational new drug) candidate selection, we conduct a preliminary solid form screen with a goal of finding a suitable solid form that can be used for PK and toxicology studies. Before the first batch of GMP material is produced, we conduct a full solid form screen to select the right solid form for clinical development. An extensive screen is carried out before drug launch with a goal of searching for and patenting all potential forms of the drug molecule. In such a way, the balance between investment in R&D and the potential of commercial success is optimized.

2. We utilize a variety of modern analytical techniques to identify and characterize solid forms. The state-of-the-art instrumentation really impresses our clients whenever they get a chance to visit our facility. X-ray powder diffraction (XRPD) and Raman spectroscopy are powerful tools for determining polymorphism or salt/cocrystal formation, as each new crystal form typically displays a fingerprint pattern. Other methods, including Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Hot-Stage Microscopy (HSM), Scanning Electron Microscope (SEM), Nuclear Magmatic Resonance (NMR), Karl Fisher Titration (KF), IR spectroscopy, as well as Dynamic Vapor Sorption (DVS) analysis, are essential to further characterize different solid forms. The goal of characterization is to have a clear understanding of the solid forms in terms of chemical composition and physical properties.

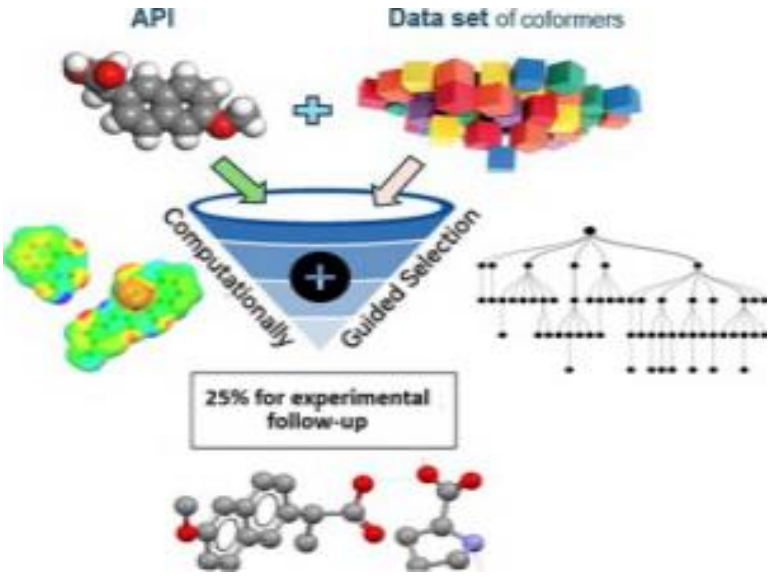


Figure 3: Virtual coformer screening model with COSMO-RS + Δ-ML,

3. We are highly skillful and experienced in determining crystal structures for key crystal forms and intermediates by single crystal diffraction or micro-crystal electron diffraction (MicroED). The crystal structure information is used not only to confirm structure for patent applications and regulatory filings, but also for understanding of structure property relationships as well as relative stability of true polymorphs. The crystal structure information may further be utilized as inputs in various predictions, such as impurity rejection, agglomeration prevention, optimization of morphology and mechanical properties. For example, we developed a method for determining absolute configuration that does not rely on the growth of large single crystals (Figure 4). By examining microcrystals formed with chiral probes, absolute configuration can be unambiguously determined by MicroED. Our streamlined method employs three steps: (1) virtual screening to identify promising chiral probes, (2) experimental cocrystal screening and (3) structure determination by MicroED and absolute configuration assignment. We successfully applied this method to analyze two chiral API molecules currently on the market for which single crystal diffraction was not used to determine absolute configuration.[4]

4. We scale up lead solid forms followed by in depth investigation of solid-state properties, including crystallinity, hygroscopicity, solubility and/or dissolution, stability, processability, & flowability. The reproducibility of the lead forms is evaluated in the scale up process with limited process development. The hygroscopicity and potential hydrate formation is accessed by dynamic vapor absorption. We determine kinetic solubility of lead solid forms in water and biorelevant media as a function of time, which provides information whether a salt/cocrystal enhances solubility as compared to the free form and if salt/cocrystal dissociation occurs during the testing. We also access solid state stability of lead forms under ICH stability conditions.

5. We investigate crystal form relationships and establish form phase maps. We determine whether two true polymorphs are monotropically or enantiotropically related. If they are enantiotropic, the transition temperature is determined. We also investigate the critical water activity between the most thermodynamically stable anhydrate and hydrates. In addition, we also access the dehydration/desolvation temperature and kinetics for hydrate/solvate. The risk of phase conversion is evaluated when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray drying, and compaction as well as exposure to stability conditions, such as humidity and temperature. This information will provide guidance for the operation space of crystallization process as well as drying and storage conditions. For instance, a phase map of a drug molecule Compound A is shown in Figure 5, indicating Form C is the most thermodynamically stable anhydrous form under ambient conditions. On the other hand, in MeOH, Form II was found to be the most thermodynamically stable solvate form. This phase mapping really provided insight on how to produce the target metastable anhydrate Form A. In another example (Figure 6), we investigate the retention or rearrangement of crystal structures over the transitions of channel hydrates. Hydrate 3 exhibits a characteristic feature of channel hydrate that involves symmetric lattice relaxation. In contrast, Hydrate 2 results in a potentially new unit cell upon dehydration due to asymmetric lattice relaxation, which converted back to Hydrate 2 in presence of water, a unique behavior for a channel hydrate rarely observed.

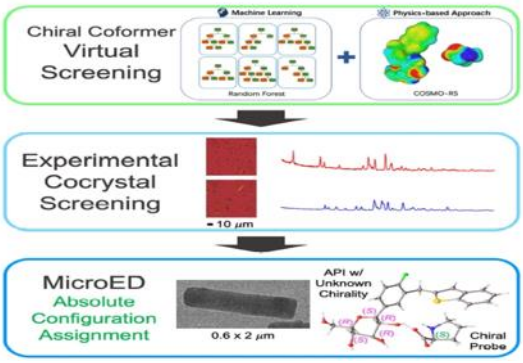


Figure 4: Workflow of absolution configuration determination by cocrystal formation

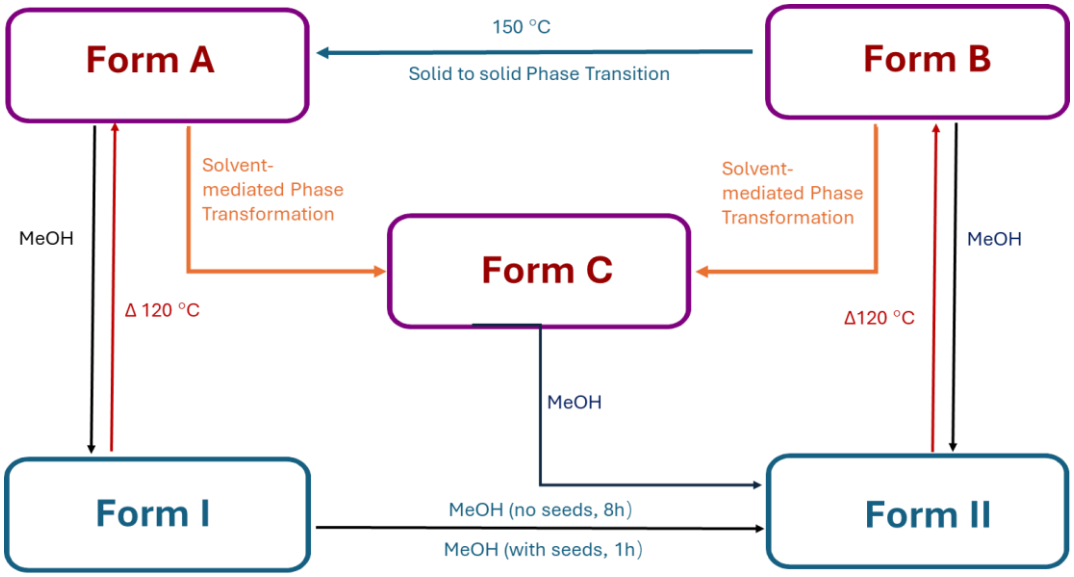


Figure 5: Crystal Form Phase Map of Compound A

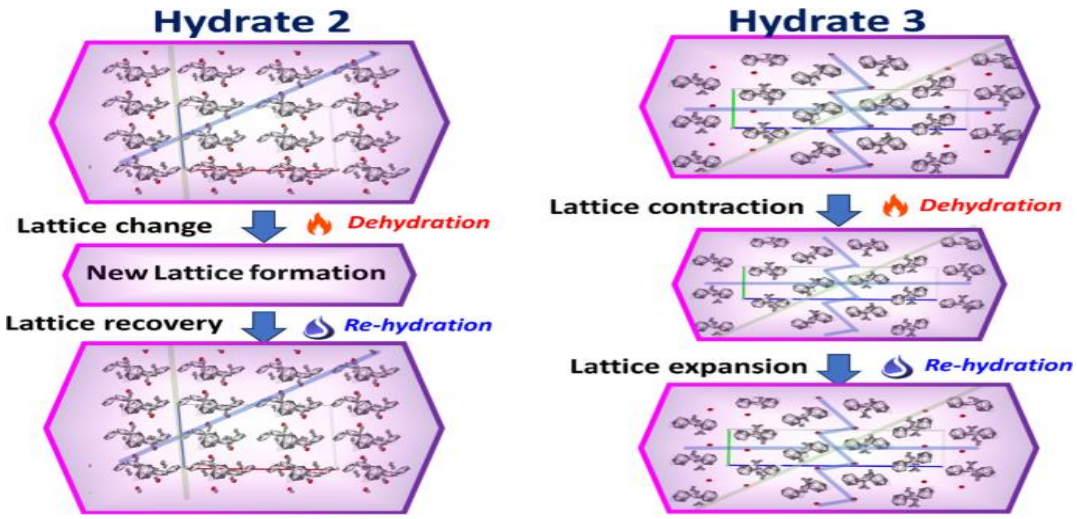


Figure 6: Phase Transitions of Channel Hydrates

6.We make the final solid form recommendation based on the optimal solid-state properties. We utilize a table matrix approach to make head-to-head comparison of the solid-state properties for lead solid forms. Our rich experience in preformulation, crystallization process development, particle engineering and DS-DP co-processing also facilitates the first-time right form selection process. A solid form screening and selection decision tree we utilize is shown in Figure 7.

Normally, we start with a polymorph screen of the free form of an API molecule, if the drug candidate is BCS class 1 or 3. The free form can be a free base, a free acid or a neutral compound. It is most desirable to find a form with acceptable solid-state properties for the API free form. If it is a BCS class 2 or 4 compound with solubility issue, we may go directly to salt screen or cocrystal screen. If no suitable form is found for the free form, we will determine if the compound is feasible for salt formation. If yes, we will conduct a salt screen to search for crystalline salt. Once a lead salt is identified, a polymorph screen will be followed up to find the most optimal crystal form of that particular salt. On the other hand, if the compound is not feasible for salt formation, or a salt screen does not end up with an acceptable salt form, we will proceed to a cocrystal screen. Once a crystalline cocrystal is discovered, a polymorph screen will be pursued to find the most optimal crystal form of the particular cocrystal. If a cocrystal screen is not successful, we may consider a screen for amorphous solid dispersion.

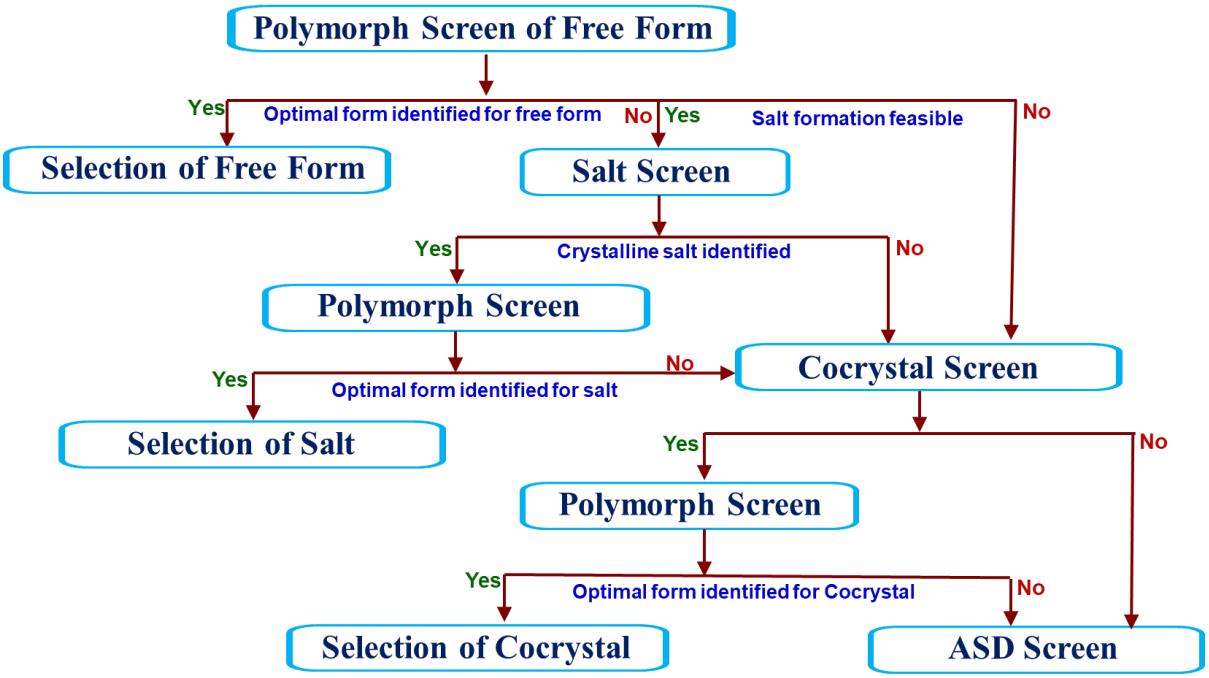


Figure 7: Solid form screening and selection decision tree

# Summary

Headed by science-centric subject matter experts, the Crystallization R&D at Porton J-Star is recognized as industry preferred partner in solid form screen and selection, crystallization process development, preformulation, particle engineering and DS-DP co-processing. Applying over 200 years of cumulative experience in globally recognized large pharma and CRO, our subject matter experts and scientists take pride in offering effective solutions to CMC challenges in solid form and crystallization process development to help bridge the gap between drug substance and drug product development. The solutions offered are scientifically driven with a dedication to the mechanistic understanding of the fundamentals. Our dedicated scientists pay great attention to understanding your project's needs and constraints. We utilize our expertise and experience to deliver molecule specific solutions appropriate to the phase of development.

References

1. Tandon R.; Tandon N., Thapar R. K., Pharm. Pat. Anal. ***2018***, 7, 59–63

2. Shah, H. S.; Michelle, C.; Xie, T.; Chaturvedi, K.; Kuang, S.; Abramov, Y. A. Pharm. Res. ***2023***, 40, 2779-2789.

3. Abramov, Y. A.; Shah, H. S.; Michelle, C.; Wan, Z.; Xie, T.; Kuang, S.; Wang, J.; Cryst. Growth Des. ***2025***, 25, DOI: 10.1021/acs.cgd.5c00160

4. Shah, H. S., Yuan J.; Xie T.; Yang Z.; Chang C.; Greenwell C.; Zeng Q.; Sun G.; Read B. N.; Wilson H. U. V.; Kuang S.; Wang, J. Sekharan S.; Bruhn J. F. Chem. Eur. J. ***2023***, 29, e202203970

5. Kuang, S., Shah, H. S.; Zhao, B. Pharm. Res. ***2024***, 41, 1533-1541.

## Shanming Kuang, Ph.D.

VP of Crystallization R&D, Porton J-STAR

25+ Years Exp. in form studies, crystallization process development and developability assessment for more than 600 small molecule drug candidates.

## Harsh S. Shah, Ph.D.

Assistant Director of Porton J-STAR

He worked at the Lachman Institute (with the FDA), Bristol Myers Squibb, Triclinic Labs and Vertex Pharmaceuticals. He got project management experience at Amneal Pharmaceuticals.

## Fei Sheng, Ph.D.

Senior Director

10+ Years of Research and Industrial exp. in Solid State Study, Crystallization, Process and Particle Engineering Development

Exp at A*STAR, Singapore

Ph.D. from Univ. of Leeds, UK, Postdoc at Leeds Univ.



Porton Pharma Solutions Ltd.
www. portonpharma.com
business@portonpharma.com